Risk, Types, and Severity of Intracranial Hemorrhage in Patients With Symptomatic Carotid Artery Stenosis

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Background and Purpose—We sought to report the occurrence and risk factors of intracranial hemorrhage during long-term follow-up of patients with internal carotid artery stenosis, with and without carotid endarterectomy.

Methods—From the prospective data of the North American Symptomatic Carotid Endarterectomy Trial, 3 types of intracranial hemorrhage were recognized: petechiae within infarction (PTI), intracerebral hematoma (ICH), and subarachnoid hemorrhage (SAH). The 30-day and 5-year risks of intracranial hemorrhage (PTI or ICH) were estimated from Kaplan-Meier event-free survival curves. Cox proportional-hazards regression modeling was used to identify risk factors.

Results—Of 1039 strokes that occurred in 749 of 2885 patients during an average follow-up of 5 years, there were 24 PTIs, 14 ICHs, and 1 SAH. The 5-year risk of intracranial hemorrhage was 1.7% in both medically and surgically treated patients, but the 30-day risk of 0.64% in surgically treated patients was 10 times higher than the risk of 0.07% in medically treated patients (P <0.01). Approximately 50% of all intracranial hemorrhages were either disabling or fatal, and ICHs were more likely to be fatal than PTIs. Old age, a history of hypertension, intermittent claudication and smoking, and infarct on brain images were risk factors for intracranial hemorrhage in medically treated patients, whereas diabetes mellitus was the sole risk factor in surgically treated patients.

Conclusions—Intracranial hemorrhages are uncommon in patients with internal carotid artery stenosis but are associated with high mortality and morbidity. The risk factors for intracranial hemorrhage are different between medically and surgically treated patients. (Stroke. 2003;34:1847-1851.)

Key Words: carotid endarterectomy • carotid stenosis • intracerebral hemorrhage

Strokes in patients with symptomatic internal carotid artery stenosis are mostly nonhemorrhagic, and intracranial hemorrhages are uncommon.1 There is little information on the occurrence and types of intracranial hemorrhage during long-term follow-up of patients with symptomatic internal carotid artery stenosis, with and without carotid endarterectomy. Previous studies have not differentiated between the types of hemorrhages and have largely described them as perioperative or postoperative complications, with reported incidence rates between 0.3% and 2.0%.2-10 Intracranial hemoranges can be subclassified as secondary petechiae within a bland cerebral infarct (PTI), intracerebral hematoma (ICH), and subarachnoid hemorrhage (SAH).11,12 PTI has also been referred to in the literature as hemorrhagic transformation, or secondary hemorrhage into an infarction, and ICH as primary intracerebral hemorrhage. The occurrence of ICH is generally twice as common as that of SAH. Population-based studies have estimated the world-standardized annual incidence of ICH to be ~15 per 100 000 people and for SAH to be 6 per 100 000 people.13-15

Different types of intracranial hemorrhage might be associated with different vascular risk factors, because the pathogenic mechanisms are not identical. Observational and epidemiological studies have indicated arterial hypertension as the most important pathogenic factor for ICH,16 and internal carotid artery stenosis might theoretically protect the ipsilateral cerebral hemisphere from the systemic arterial pressure. ICH and hypertensive encephalopathy have been reported to be the acute complications of carotid endarterectomy, especially in patients with severe stenosis or poorly controlled hypertension.2-10,17-24 In contrast, observational studies and clinical trials have implicated therapeutic thrombolysis, systemic anticoagulation, antiplatelet agents, large cerebral infarction, and embolic strokes as the risk factors for PTI.25-32

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The aim of the present study was to determine the occurrence of different types of intracranial hemorrhage during early and long-term follow-up of patients with symptomatic internal carotid artery stenosis, with and without carotid endarterectomy. Risk factors associated with the occurrence of intracranial hemorrhage were also assessed. Data were taken from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Patients and Methods
The NASCET was a randomized, multicenter, clinical trial designed to determine the efficacy of carotid endarterectomy among patients with symptomatic internal carotid artery stenosis. Patients were enrolled in the trial if they had had a focal retinal or hemispheric transient ischemic attack or a nondisabling focal retinal or hemispheric ischemic stroke related to carotid artery stenosis within 180 days of randomization.

From December 1987 to December 1996, patients were randomized to best medical care (n=1449) or best medical care plus carotid endarterectomy (n=1436) and were followed up until the end of December 1997. Details of the methods and final results have been published. Patients were ineligible if they had a probable cardiac source of embolism or serious disease likely to cause death within 5 years. All patients had a detailed medical examination at baseline, including an electrocardiogram and chest x-ray. Computed tomographic (CT) or magnetic resonance imaging of the brain was performed to determine the presence of infarcts and to rule out other causes for hemispheric symptoms. The degree of internal carotid artery stenosis was measured from a conventional carotid angiogram according to strict criteria.

During follow-up, a trial neurologist examined the patients at 30 days; at 3, 6, 9, and 12 months; and every 4 months thereafter. All patients received antithrombotic treatment, generally aspirin, and when indicated, antihypertensive and antilipemic drugs and were advised to stop smoking. The territory and type of stroke during follow-up were centrally reviewed, as was the level of disability. The trial neuroradiologist centrally reviewed the poststroke cross-sectional brain images. Strokes were classified as disabling if a patient had a modified Rankin score of 3 or more at 90 days after the operation. Each ischemic stroke was designated as to its cause: large artery, lacunar, or cardioembolic. Lacunar strokes were defined by using classic lacunar syndromes, with or without radiological deep lesions no more than 1 cm in diameter. Cardioembolic strokes were defined by a combination of clinical and echocardiographic criteria. Ischemic strokes without a lacunar or cardioembolic origin were classified as large-artery strokes. Some ischemic strokes were designated as PTI, identified by secondary bleeding within a bland cerebral infarct, or a petechial, curvilinear, cortical, or focal hemorrhage within an acute infarct on brain imaging studies. Hemorrhages were classified as ICH when a hematoma was observed with mass effect on the adjacent brain, and SAH was identified when the bleeding occurred mainly in the subarachnoid space.

The 30-day and 5-year risks of intracranial hemorrhage (PTI or ICH) were estimated from Kaplan-Meier event-free survival curves. The present study used on-treatment analyses: patients who changed treatment group or had carotid endarterectomy on the side opposite that of the randomized internal carotid artery during follow-up had their data censored at the date of crossover. Differences in the risks between groups were assessed for statistical significance by the logrank test. Multivariable Cox proportional-hazards regression modeling was used to identify patient characteristics that increased the risk of intracranial hemorrhage (PTI or ICH).

Results
The median age of the patients in the NASCET was 67 years, and 70% were male. A history of hypertension was reported in 61% of the patients, diabetes mellitus in 22%, myocardial infarction in 20%, intermittent claudication in 15%, and smoking in the past year in 42%. Presence of severe (≥70%) internal carotid artery stenosis was noted in 23% of the patients and brain infarcts in 44% on the side of the ischemic symptoms. Antithrombotic medications were taken by ≈97% (86% aspirin, 11% other) of the patients throughout the duration of the trial.

Of 1039 strokes that occurred in 749 of 2885 patients during an average follow-up of 5 years, 983 were nonhemorrhagic and 56 (5.4%) were hemorrhagic: 34 PTIs, 21 ICHs, and 1 SAH. The numbers of intracranial hemorrhages used in the on-treatment analyses were 24 PTIs, 14 ICHs, and 1 SAH. The 5-year risk of intracranial hemorrhage (PTI or ICH) in medically treated patients was 1.7%, identical to the 1.7% risk for surgically treated patients (Table 1). However, the 30-day risk of 0.64% in surgically treated patients was 10 times higher than the risk of 0.07% in medically treated patients (P=0.01, medical versus surgical treatment). The increased perioperative risk of intracranial hemorrhage, with convergence at 5 years, is illustrated in Figure 1 and separately for the outcomes of PTI (Figure 2a) and ICH (Figure 2b).

| TABLE 1. 30-Day and 5-Year Risks (%) of Intracranial Hemorrhage |
|-----------------|-----------------|-----------------|
|                  | Medical Group    | Surgical Group   | P    |
|                  | (n=1449)         | (n=1436)         |      |
| 30-day risk      |                 |                 |      |
| Any intracranial hemorrhage | 0.07 (1)         | 0.64 (9)         | 0.01 |
| Petechiae within infarction | 0.00 (0)         | 0.42 (6*)        | 0.01 |
| Intracerebral hematoma | 0.07 (1)         | 0.22 (3†)        | 0.30 |
| 5-year risk      |                 |                 |      |
| Any intracranial hemorrhage | 1.7 (17)         | 1.7 (21)         | 0.74 |
| Petechiae within infarction | 1.2 (12)         | 1.0 (12)         | 0.80 |
| Intracerebral hematoma | 0.5 (5)          | 0.7 (9)          | 0.38 |

The number in parentheses denotes the number of events.

*All 6 infarctions occurred intraoperatively, with petechiae noted on a follow-up CT scan, 1 to 7 days postoperatively.
†The intracerebral hematomas were detected on days 1, 6, and 8, postoperatively.

Figure 1. Kaplan-Meier freedom from intracranial hemorrhage curves (PTI or ICH). Surgically treated patients had a higher risk of intracranial hemorrhage within 30 days after carotid endarterectomy than did medically treated patients (P=0.01), but the long-term risk was similar in the 2 groups (P=0.74).
The cause of PTI was predominantly of large-artery origin, with 29.2% of the PTIs attributable to a cardioembolic source (Table 2). Approximately 50% of all intracranial hemorrhages were either disabling or fatal (Table 2). ICHs were more likely to be fatal than PTIs. PTIs occurred in a variety of sites in the cortical and subcortical regions of the cerebrum and cerebellum. ICHs occurred in a variety of sites in the thalamus, basal ganglia, cerebellum, and white matter of the hemispheres. PTIs and ICHs did not appear to be related to aspirin dose (Table 3).

Of the 85 strokes that occurred within 30 days of surgery, 10 (11.8%) were hemorrhagic (Table 4). Of the 10 strokes, 6 occurred intraoperatively. Petechiae were noted on a follow-up CT scan 1 to 7 days postoperatively, and therefore, all 6 were designated as PTI. The 3 ICHs were detected on postoperative days 1, 6, and 8, and 1 SAH occurred on day 6. Of the 6 patients with a PTI, 1 had a clamp-site injury, another had thrombosis at the endarterectomy site on reexploration, and the remaining 4 patients had normal arteries. All 3 patients with ICH had delayed onset of symptoms after an uneventful endarterectomy on their severely stenosed internal carotid artery, and the operated arteries were normal on postsurgical evaluation. There was no apparent relation between the use of heparin and its reversal, the use of a shunt, average intraoperative blood pressure, and the occurrence of intracranial hemorrhage in comparison with a nonhemorrhagic stroke within 30 days after endarterectomy (Table 4).

The single patient with a delayed SAH, after an uneventful endarterectomy, had two 4-mm ipsilateral intracranial aneurysms found on baseline angiography. The cause of the

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**TABLE 2. Cause and Severity of Intracranial Hemorrhage**

<table>
<thead>
<tr>
<th>Cause of stroke</th>
<th>PTI (n=24) (%)</th>
<th>ICH (n=14) (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery</td>
<td>70.8</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>29.2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Severity of stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondisabling</td>
<td>50.0</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td>Disabling</td>
<td>33.3</td>
<td>28.6</td>
<td>0.69</td>
</tr>
<tr>
<td>Fatal</td>
<td>16.7</td>
<td>28.6</td>
<td></td>
</tr>
</tbody>
</table>

PTI indicates petechiae within infarction; ICH, intracerebral hematoma.

*P value refers to the overall association between hemorrhage type and severity of stroke.

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**TABLE 3. Antithrombotics in Patients with Intracranial Hemorrhage**

<table>
<thead>
<tr>
<th>Antithrombotic Agent</th>
<th>PTI (n=24) (%)</th>
<th>ICH (n=14) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1 (4.2)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Aspirin 100–325 mg</td>
<td>11 (45.8)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Aspirin 975–1300 mg</td>
<td>8 (33.3)</td>
<td>5 (35.8)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4 (16.7)</td>
<td>1 (7.1)</td>
</tr>
</tbody>
</table>

PTI indicates petechiae within infarction; ICH, intracerebral hematoma.

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**TABLE 4. Details of Intracranial Hemorrhages and Nonhemorrhagic Strokes Within 30 Days after Carotid Endarterectomy**

<table>
<thead>
<tr>
<th></th>
<th>PTI (n=6) (%)</th>
<th>ICH (n=3) (%)</th>
<th>Nonhemorrhagic (n=75) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of heparin, U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5000</td>
<td>2 (33.3)</td>
<td>1 (33.3)</td>
<td>11 (14.7)</td>
</tr>
<tr>
<td>5000</td>
<td>2 (33.3)</td>
<td>2 (66.7)</td>
<td>31 (41.3)</td>
</tr>
<tr>
<td>&gt;5000</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>33 (44.0)</td>
</tr>
<tr>
<td>Heparin reversed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (83.3)</td>
<td>1 (33.3)</td>
<td>46 (61.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (16.7)</td>
<td>2 (67.7)</td>
<td>29 (38.7)</td>
</tr>
<tr>
<td>Shunt used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (83.3)</td>
<td>3 (100.0)</td>
<td>43 (57.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>32 (42.7)</td>
</tr>
<tr>
<td>Average intraoperative BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP≤140 and DBP≤80</td>
<td>5 (83.3)</td>
<td>2 (66.7)</td>
<td>52 (69.3)</td>
</tr>
<tr>
<td>SBP&gt;140 or DBP&gt;80</td>
<td>1 (16.7)</td>
<td>1 (33.3)</td>
<td>23 (30.7)</td>
</tr>
</tbody>
</table>

PTI indicates petechiae within infarction; ICH, intracerebral hematoma; SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg).

Note: There was one other patient who had a subarachnoid hemorrhage on day 6 after surgery.
bleeding into the basal cisterns was not identified. At autopsy, serial sectioning failed to identify any areas of rupture or inflammatory reaction in these aneurysms.

Relations between patient characteristics and risk of intracranial hemorrhage differed between medically and surgically treated patients. Age ≥75 years increased the risk of intracranial hemorrhage 6-fold in medically treated patients (P<0.001) but had little effect in surgically treated patients (Table 5). History of hypertension, intermittent claudication, smoking in the past year, and infarct on brain imaging doubled the risk of intracranial hemorrhage in medically treated patients but not in the surgical group, although this difference was not statistically significant. A history of diabetes mellitus was the only patient characteristic that markedly increased the risk of intracranial hemorrhage by 2.8 times in surgically treated patients (P=0.02). All other hazard ratios were statistically nonsignificant and near unity.

### Discussion

The present study confirmed that intracranial hemorrhages are uncommon among patients with symptomatic internal carotid artery stenosis, with or without carotid endarterectomy, despite almost universal use of antithrombotic medications in a large number of patients during an average follow-up of 5 years. There was no apparent relation to the dose of aspirin. Although their occurrence is uncommon, intracranial hemorrhages are serious events that are likely to be disabling or fatal. The sites of PTI and ICH in the brain are variable and unaffected by endarterectomy.

Patients with internal carotid artery stenosis are at risk of stroke from a variety of causes. Carotid endarterectomy cannot prevent all ischemic strokes of lacunar or any of cardioembolic origin or hemorrhages, and so the 5-year risk of an ICH was similar between medically and surgically treated patients. On the other hand, carotid endarterectomy produced a 10-fold increase in the 30-day risk of intracranial hemorrhage when compared with medical treatment. Over long-term follow-up, the higher initial risk of hemorrhage in surgically treated patients was offset by a lower subsequent risk of stroke of all types (including hemorrhages) when compared with medically treated patients.

An interesting finding of the present study was that the risk factors for intracranial hemorrhage (PTI or ICH) were different between medically and surgically treated patients. In surgically treated patients, diabetes mellitus was the only significant risk factor, and one can speculate that tight control of perioperative glucose levels might reduce the risk of hemorrhage. For medically treated patients, the modifiable risk factors for intracranial hemorrhage were hypertension, intermittent claudication, and smoking.

The observed number of PTIs in the present study was likely an underestimate, because the NASCET protocol did not require delayed neuroimaging or repeated neuroimaging studies. The intracranial hemorrhages were diagnosed by objective clinical and radiologic criteria: a clinical syndrome of stroke plus hemorrhagic changes on neuroimaging. The proposed mechanism of PTI is diapedesis of blood through damaged small vessels within an area of ischemic infarct during reperfusion. In contrast, ICH results from arterial rupture, with formation of a hematoma under systemic arterial pressure. Presence of the hematoma without a surrounding acute infarct on the first brain scan identified patients with an ICH.

Ten of the 11 early intracranial hemorrhages were related to carotid endarterectomy. Thrombosis or injury of the operated artery underlay 2 PTIs. Further improvement in surgical technique and perioperative management might reduce this number to zero. Results of the present study do not support the importance of heparin dosage and its reversal, use of a shunt, and intraoperative blood pressure in the occurrence of hemorrhage within 30 days of surgery. The clinical and radiologic presentation of the 3 patients with delayed onset of ICH after an uneventful endarterectomy on their severely stenosed internal carotid artery was consistent with hyperperfusion syndrome. Among patients with ≥70% stenosis of the internal carotid artery, tight control of arterial pressure throughout the perioperative and postoperative periods might reduce the risk of ICH due to hyperperfusion syndrome.

In summary, different types of intracranial hemorrhages can be defined clinicoangiologically. Intracranial hemorrhages were uncommon during long-term follow-up of patients with symptomatic internal carotid artery stenosis but were associated with high mortality and morbidity. Improvement in surgical techniques and perioperative management might reduce the perioperative risk of intracranial hemorrhage. This study provides a useful set of observations to compare with the complications that will occur in the emerging strategy of carotid angioplasty and stenting.

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